Health Canada Santé Canada

Therapeutic Products Directorate

Health Products and Food Branch

Direction des produits thérapeutiques

Direction générale des produits de santé et des aliments




Deficiencies in (A)NDSs and S(A)NDSs at TPD

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Presentation Overview

- Analysis of Notices of Deficiency and Notices of Non-Compliance
  - background
  - scope
  - data collected
- Common deficiencies in (S)(A)NDSs
  - safety and efficacy
  - quality
- Next steps
  - TPD
  - submission sponsors

Analysis of Notices of Deficiency and Notices of Non-Compliance (1)

- Analysis of reasons for NONs and NODs requested by TPD Director General
- Analysis included all NODs (23) and NONs (140) issued in 2005
- 44 companies received NODs/NONs; the top 6 companies received 79 (48%) of the NODs/NONs

Analysis of Notices of Deficiency and Notices of Non-Compliance (2)

- Breakdown of NODs/NONs issued:
  - 98 ANDSs
  - 5 SANDSs
  - 27 NDSs
  - 33 SNDSs
- 63% of the NODs/NONs issued were for abbreviated submissions, but these made up only about 45% of the submissions received

Common deficiencies in (S)(A)NDSs: Safety and Efficacy (1)

- **Incomplete supportive data (1)**
  - **missing text, tables, charts, patient listings, appendices**
  - **missing pre-clinical information**
  - **missing clinical study reports and efficacy summaries**
  - **lack of explanation for the inclusion or exclusion of data in either pharmacokinetic and/or statistical analysis**

Common deficiencies in (S)(A)NDSs: Safety and Efficacy (2)

- **Incomplete supportive data (2)**
  - **lack of evidence for long-term use (when seeking long-term indication)**
  - **failing to identify studies to be considered pivotal**
  - **lack of information or discussion on the comparative safety and efficacy profile of the product compared to other marketed drugs**

Common deficiencies in (S)(A)NDSs: Safety and Efficacy (3)

- **Methodological issues (1)**
  - **primary efficacy parameters not reaching statistical significance**
  - **new primary efficacy parameters being introduced through amendments**
  - **lack of definition of primary efficacy outcomes which leads to a clinical and statistical concern**

Common deficiencies in (S)(A)NDSs: Safety and Efficacy (4)

- **Methodological issues (2)**
  - **inappropriate pooling of primary efficacy results of multiple strata to produce an overall estimate**
  - **concerns over the secondary efficacy parameter (particularly when related to primary parameter and part of pivotal trial)**

Common deficiencies in (S)(A)NDSs: Safety and Efficacy (5)

- **Methodological issues (3)**
  - **concerns over determination of clinical equivalence**
  - **underpowered statistical analysis**
  - **statistical significance mainly driven by one component**
  - **generalizability of the results obtained in the studies is limited to the dose regimen used**

Common deficiencies in (S)(A)NDSs: Safety and Efficacy (6)

- **Methodological issues (4)**
  - **concerns about selected patient population**
  - **patients not assessed in accordance with study protocol**
  - **concerns about study design**

Common deficiencies in (S)(A)NDSs: Safety and Efficacy (7)

- **Efficacy issues**
  - **lack of a dose-response effect**
  - **lack of efficacy data on appropriate dosage of product**
  - **results were statistically but not clinically significant**
  - **lack of statistical power**

Common deficiencies in (S)(A)NDSs: Safety and Efficacy (8)

- **Safety issues**
  - **inadequate long-term safety**
  - **insufficient exposure data**
  - **limited safety assessments**
  - **safety parameters of great interest (such as QTc prolongation)**

Common deficiencies in (S)(A)NDSs: Quality (1)

- **Drug substance manufacturing**
  - **incomplete information on the starting material (e.g. information on synthetic process, certificate of analysis missing)**
  - **insufficient detail on the synthetic process for the drug substance (e.g. information on reagents, solvents, reaction conditions missing)**

Common deficiencies in (S)(A)NDSs: Quality (2)

- **Drug product manufacturing**
  - **incomplete process validation protocols (e.g. critical process parameters not identified, inadequate acceptance criteria)**
  - **incomplete blank manufacturing documents (e.g. not provided for each strength, inadequate description of equipment)**

Common deficiencies in (S)(A)NDSs: Quality (3)

- Characterization of impurities in drug substance and drug product
  - terminology inconsistent with guidance on impurities
  - proposed limits for individual impurities not in accordance with guidance on impurities

Common deficiencies in (S)(A)NDSs: Quality (4)

- Control of drug substance and drug product
  - system suitability and/or validation of analytical procedures inadequate
  - batch analyses incomplete

Next Steps: TPD

- Complete data analysis
- Work with review areas to determine which issues are “NOD/NON issues”
- Review available guidance documents for the need to develop / finalize / update

Next Steps: Submission Sponsors

- Follow guidance documents
- Learn from past submissions
- Use pre-submission meetings
- Contact TPD with concerns regarding
  - lack of guidance
  - inconsistent guidance application / reviews (within TPD and internationally)
  - lack of communication on individual submissions

Thank you for your attention.

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